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NEWS 4	JUL 02	CHEMCATS accession numbers revised
NEWS 5	JUL 02	CA/CAplus enhanced with utility model patents from China
NEWS 6	JUL 16	CAplus enhanced with French and German abstracts
NEWS 7	JUL 18	CA/CAplus patent coverage enhanced
NEWS 8	JUL 26	USPATFULL/USPAT2 enhanced with IPC reclassification
NEWS 9	JUL 30	USGENE now available on STN
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NEWS 13	AUG 20	CA/CAplus enhanced with CAS indexing in pre-1907 records
NEWS 14	AUG 27	Full-text patent databases enhanced with predefined patent family display formats from INPADOCDB
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NEWS 17	SEP 07	STN AnaVist, Version 2.0, now available with Derwent World Patents Index
NEWS 18	SEP 13	FORIS renamed to SOFIS
NEWS 19	SEP 13	INPADOCDB enhanced with monthly SDI frequency
NEWS 20	SEP 17	CA/CAplus enhanced with printed CA page images from 1967-1998
NEWS 21	SEP 17	CAplus coverage extended to include traditional medicine patents
NEWS 22	SEP 24	EMBASE, EMBAL, and LEMBASE reloaded with enhancements
NEWS 23	OCT 02	CA/CAplus enhanced with pre-1907 records from Chemisches Zentralblatt
NEWS 24	OCT 19	BEILSTEIN updated with new compounds
NEWS 25	NOV 15	Derwent Indian patent publication number format enhanced
NEWS 26	NOV 19	WPIX enhanced with XML display format

NEWS EXPRESS 19 SEPTEMBER 2007: CURRENT WINDOWS VERSION IS V8.2, CURRENT MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP), AND CURRENT DISCOVER FILE IS DATED 19 SEPTEMBER 2007.

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FILE LAST UPDATED: 28 Nov 2007 (20071128/ED)

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=> s muscarinic receptor?
         26397 MUSCARINIC
            13 MUSCARINICS
         26399 MUSCARINIC
                  (MUSCARINIC OR MUSCARINICS)
        867947 RECEPTOR?
L1       17665 MUSCARINIC RECEPTOR?
                  (MUSCARINIC(W)RECEPTOR?)

=> s l1 and respitory?
             4 RESPITORY?
L2           0 L1 AND RESPITORY?

=> s l1 and respiratory?
        130549 RESPIRATORY?
L3         468 L1 AND RESPIRATORY?

=> s l3 and antagonism?
         42203 ANTAGONISM?
L4          21 L3 AND ANTAGONISM?

=> d ibib abs tot
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L4 ANSWER 1 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1217606 CAPLUS
DOCUMENT NUMBER: 144:210164
TITLE: Muscarinic receptors, leukotriene B4 production and neutrophilic inflammation in COPD patients
AUTHOR(S): Profita, M.; Di Giorgi, R.; Sala, A.; Bonanno, A.; Riccobono, L.; Mirabella, F.; Gjomarkaj, M.; Bonsignore, G.; Bousquet, J.; Vignola, A. M.
CORPORATE SOURCE: Italian National Research Council, Institute of Biomedicine and Molecular Immunology, Palermo, Italy
SOURCE: Allergy (Oxford, United Kingdom) (2005), 60(11), 1361-1369
CODEN: LLRGDY; ISSN: 0105-4538
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

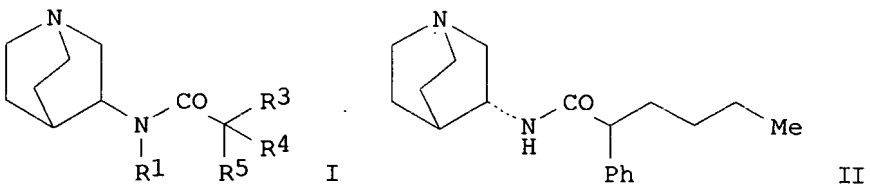
AB Background: Acetylcholine (ACh) plays an important role in smooth muscle contraction and in the development of airway narrowing; preliminary evidences led us to hypothesize that ACh might also play a role in the development of airways inflammation in chronic obstructive pulmonary disease (COPD). Methods: We evaluated the concns. of leukotriene B4 (LTB4) in induced sputum, and the expression of Ach M1, M2, and M3 receptors in sputum cells (SC) obtained from 16 patients with COPD, 11 smokers, and 14 control subjects. The SC were also treated with ACh and the production of LTB4 assessed in the presence or absence of a muscarinic antagonist (oxitropium). In blood monocytes, we evaluated LTB4 release and activation of the extracellular signal-regulated kinases (ERK) pathway after treatment with Ach. Results: The LTB4 concns. were higher in COPD than in controls ($P < 0.01$) and correlated with the number of neutrophil ($P < 0.01$). The M3 receptors expression was increased in COPD subjects when compared to smokers and control ($P < 0.05$ and 0.0001, resp.), while M2 expression resulted decreased ($P < 0.05$ and 0.01). The ACh-induced LTB4 production was observed in peripheral blood monocytes, and was sensitive to ERK inhibition. Similarly, ACh significantly increased neutrophil chemotactic activity and LTB4 released from SC of COPD patients only, and these effects were blocked by pretreatment with the inhibitor of ERK pathway PD98059. Conclusions: The results obtained show that muscarinic receptors may be involved in airway inflammation in COPD subjects through ACh-induced, ERK1/2-dependent LTB4 release. Muscarinic antagonism may contribute to reduce neutrophil infiltration and activation in COPD.

REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:41467 CAPLUS
DOCUMENT NUMBER: 140:94180
TITLE: Preparation of new quinuclidine amide derivatives for therapeutic uses as antagonists of M3 muscarinic receptors
INVENTOR(S): Prat Quinones, Maria
PATENT ASSIGNEE(S): Almirall Prodesfarma S.A., Spain
SOURCE: PCT Int. Appl., 65 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005285	A1	20040115	WO 2003-EP6708	20030625
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
ES 2204295	A1	20040416	ES 2002-1539	20020702
ES 2204295	B1	20050801		
CA 2492535	A1	20040115	CA 2003-2492535	20030625
AU 2003242757	A1	20040123	AU 2003-242757	20030625
EP 1519933	A1	20050406	EP 2003-762514	20030625
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
BR 2003012216	A	20050412	BR 2003-12216	20030625
CN 1678610	A	20051005	CN 2003-820648	20030625
JP 2005533826	T	20051110	JP 2004-518575	20030625
NZ 537341	A	20060428	NZ 2003-537341	20030625
MX 2004PA12271	A	20050408	MX 2004-PA12271	20041207
ZA 2004010404	A	20050905	ZA 2004-10404	20041223
IN 2004DN04140	A	20061229	IN 2004-DN4140	20041227
NO 2005000164	A	20050404	NO 2005-164	20050112
US 2006167042	A1	20060727	US 2005-518714	20050801
PRIORITY APPLN. INFO.:			ES 2002-1539 A	20020702
			WO 2003-EP6708 W	20030625

OTHER SOURCE(S): MARPAT 140:94180
GI



AB N-quinuclidinyl amides, such as I [R1 = H, alkyl; R3 = furyl, thienyl, phenyl; R4 = alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylmethyl, Ph, benzyl, phenethyl, furyl, thienyl; R5 = H, OH, Me, CH2OH], were prepared for use in therapy as antagonists of M3 muscarinic receptors

. These amides are claimed for use in the treatment of respiratory, urol. or gastrointestinal pathol. conditions and diseases susceptible to amelioration by antagonism of M3 muscarinic receptors. Thus, amide II was prepared in 63.1% yield via an amidation reaction of (3R)-aminoquinuclidine with 2-phenylhexanoic acid in DMF and CHCl3. The prepared N-quinuclidinyl amides were assayed for human muscarinic receptor binding activity and for effect on bronchial response to i.v. acetylcholine challenge in guinea pigs. Tablet, liquid inhalant, powder inhalant, and inhalation aerosol pharmaceutical compns. of the amides were presented.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:869967 CAPLUS
DOCUMENT NUMBER: 140:139608
TITLE: Contractile role of M2 and M3 muscarinic receptors in gastrointestinal, airway and urinary bladder smooth muscle
AUTHOR(S): Ehlert, Frederick J.
CORPORATE SOURCE: College of Medicine, Department of Pharmacology, University of California, Irvine, Irvine, CA, 92697-4625, USA
SOURCE: Life Sciences (2003), 74(2-3), 355-366
CODEN: LIFSAK; ISSN: 0024-3205
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Both M2 and M3 muscarinic receptors are expressed in smooth muscle and influence contraction through distinct signaling pathways. M3 receptors interact with Gq to trigger phosphoinositide hydrolysis, Ca2+ mobilization and a direct contractile response. In contrast, M2 receptors interact with Gi and Go to inhibit adenylyl cyclase and Ca2+-activated K+ channels and to potentiate a Ca2+-dependent, nonselective cation conductance. Ultimately, these mechanisms lead to the prediction that the influence of the M2 receptor on contraction should be conditional upon mobilization of Ca2+ by another receptor such as the M3. Math. modeling studies of these mechanisms show that the competitive antagonism of a muscarinic response mediated through activation of both M2 and M3 receptors should resemble the profile of the directly acting receptor (i.e., the M3) and not that of the conditionally acting receptor (i.e., the M2). Using a combination of pharmacol. and genetic approaches, we have identified 2 mechanisms for the M2 receptor in contraction: (1) a high potency inhibition of the relaxation elicited by agents that increase cytosolic cAMP and (2) a low potency potentiation of contractions elicited by the M3 receptor. The latter mechanism may be involved in muscarinic agonist-mediated heterologous desensitization of smooth muscle, which requires activation of both M2 and M3 receptors.
REFERENCE COUNT: 68 THERE ARE 68 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:837052 CAPLUS
DOCUMENT NUMBER: 139:337980
TITLE: Preparation of aminopyrimidines with muscarinic M3 antagonist and PDE IV inhibiting activity
INVENTOR(S): Provins, Laurent; Van Keulen, Berend Jan; Surtees, John; Talaga, Patrice; Christophe, Bernard
PATENT ASSIGNEE(S): UCB, S.A., Belg.
SOURCE: PCT Int. Appl., 71 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003087064	A1	20031023	WO 2003-EP3299	20030329
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003222786	A1	20031027	AU 2003-222786	20030329
EP 1499598	A1	20050126	EP 2003-718717	20030329
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
US 2006074068	A1	20060406	US 2005-511660	20051005
PRIORITY APPLN. INFO.:			EP 2002-8706 A	20020418
			WO 2003-EP3299 W	20030329

OTHER SOURCE(S): MARPAT 139:337980
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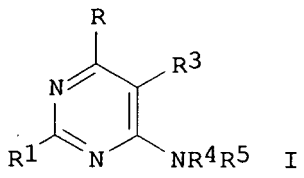

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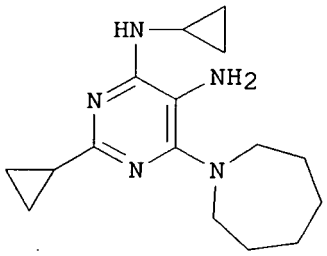


II

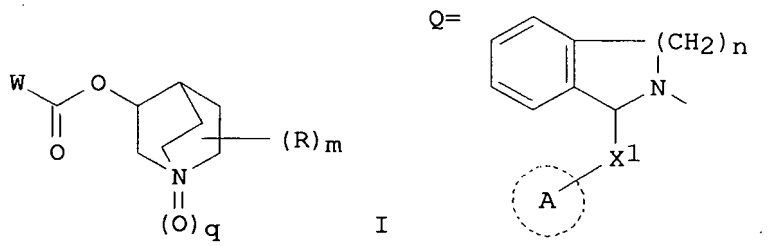
AB Aminopyrimidines I [R = NHR2, (un)substituted azetidinyl; R1 = alkyl, cycloalkyl; R2 = cycloalkyl; R3 = H, alkyl, halogen, OH, alkoxy, amino; R2R3 = alkylene; R4 = H, alkyl; R5 = cycloalkyl, aralkyl, heterocyclylalkyl; NR4R5 = heterocyclic], combining affinity and antagonism against the human M3 muscarinic receptor with activity as selective phosphodiesterase IV (PDE IV) inhibitors, were prepared Thus, the amine II was prepared from 6-chloro-N,2-dicyclopropyl-5-nitropyrimidin-4-amine by reaction with hexamethylenimine and reduction of the nitro group.
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS

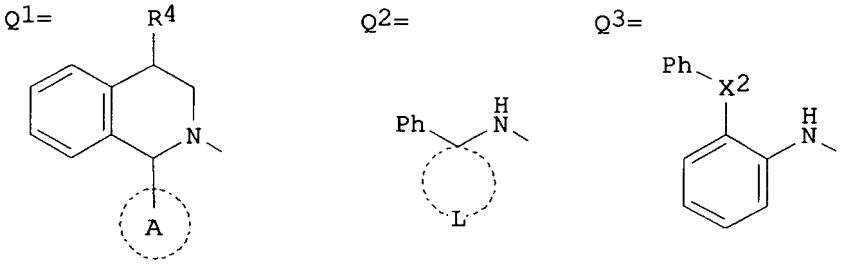
RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:750706 CAPLUS
DOCUMENT NUMBER: 139:277051
TITLE: Preparation of quinuclidine derivatives as muscarine M3 receptor antagonists
INVENTOR(S): Inakoshi, Masatoshi; Nagata, Koji; Yorimoto, Naoki; Naito, Ryo; Ikeda, Masaru; Hatanaka, Toshiki
PATENT ASSIGNEE(S): Yamanouchi Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 12 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2003267977	A	20030925	JP 2002-69621	20020314
PRIORITY APPLN. INFO.:			JP 2002-69621	20020314
OTHER SOURCE(S):	MARPAT 139:277051			

GI





AB The title compds. [I; R = halo, OR1, COR1, CO2 R1 , CON(R1)R2, S(O)pR1, NR1R2, N(R1)COR2, N(R1)CO2R2, N(R1)CON(R2)R3, N(R1)S(O)pR2, each (un)substituted lower alkyl, lower alkenyl, cycloalkyl, aryl, heteroaryl, or 5- to 6-membered ring saturated heterocyclyl; m = an integer of 1-3; q = 0, 1; wherein R1-R3 = H, each lower alkyl, lower alkenyl, cycloalkyl, aryl, heteroaryl, or 5- to 6-membered ring saturated heterocyclyl; p = 0, 1,2; W = Q-Q3, Ph2CHNH; wherein n = 1,2; the ring A = each (un)substituted aryl, cycloalkyl, heteroaryl, or 5- to 6-membered ring saturated heterocyclyl; R4 = HO, lower alkyl, lower alkoxycarbonyl; L = C2-7 alkylene optionally interrupted by O or (un)substituted NH; X1 = a single bond, CH2; X2 = a single bond, O, S], salts thereof, or N-oxides thereof or quaternary ammonium salts thereof are prepared These compds. possess muscarine M3 receptor antagonism and are useful for the treatment or prevention of urol. diseases, respiratory diseases, or digestive tract diseases. Thus, a solution of 2-ethylquinuclidin-3-ol 2.00, Et 1-phenyl-1,2,3,4-tetrahydroisoquinoline-2-carboxylate 3.68, sodium

ethoxide 0.18 g, 1.8 mL DMF in 37 mL toluene underwent reactive distillation at distillation rate of 3.7 mL/h for 8 h and was extracted with 19 mL toluene and 10 mL H2O followed by extraction of the toluene layer with 10 mL H2O and then with 5% aqueous HCl solution, adding 20 mL EtOAc and 20 mL 40% aqueous K2CO3 solution, drying the EtOAc layer over MgSO4 and evaporation under reduced pressure to give 3.6 g 2-ethylquinuclidin-3-yl 1-phenyl-1,2,3,4-tetrahydro-2-isoquinolinecarboxylate. The compds. I exhibited high affinity to muscarine M3 receptor expressed in Chinese hamster egg-derived cells (CHO-k1).

L4 ANSWER 6 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:236190 CAPLUS
DOCUMENT NUMBER: 139:317198
TITLE: A Mechanism for Rapacuronium-induced Bronchospasm: M2 Muscarinic Receptor Antagonism
AUTHOR(S): Jooste, Edmund; Klafter, Farrah; Hirshman, Carol A.; Emala, Charles W.
CORPORATE SOURCE: Dep. Anesthesiol., College of Physicians and Surgeons, Columbia Univ., New York, NY, 10032, USA
SOURCE: Anesthesiology (2003), 98(4), 906-911
CODEN: ANESAV; ISSN: 0003-3022
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A safe and effective ultra-short-acting nondepolarizing neuromuscular blocking agent is required to block nicotinic receptors to facilitate intubation. Rapacuronium, which sought to fulfill these criteria, was withdrawn from clin. use due to a high incidence of bronchospasm resulting in death. Understanding the mechanism by which rapacuronium induces fatal bronchospasm is imperative so that newly synthesized neuromuscular blocking agents that share this mechanism will not be introduced clin. Selective inhibition of M2 muscarinic receptors by muscle relaxants during periods of parasympathetic nerve stimulation (e.g., intubation) can result in the massive release METHODS of acetylcholine to act on unopposed M3 muscarinic receptors in airway smooth muscle, thereby facilitating bronchoconstriction. Competitive radioligand binding determined the binding affinities of rapacuronium, vecuronium, cisatracurium, methoctramine (selective M2 antagonist), and 4-diphenylacetoxy-N-methylpiperidine methiodide (4-DAMP; selective M3 antagonist) for M2 and M3 muscarinic receptors. Rapacuronium competitively displaced 3H-QNB from the M2 muscarinic receptors but not from the M3 muscarinic receptors within clin. relevant concns. Fifty percent inhibitory concns. (mean ± SE) for rapacuronium were as follows: M2 muscarinic receptor, 5.10±1.5 μm (n = 6); M3 muscarinic receptor, 77.9±11 μm (n = 8). Cisatracurium and vecuronium competitively displaced 3H-QNB from both M2 and M3 muscarinic receptors but had affinities at greater than clin. achieved concns. for these relaxants. Rapacuronium in clin. significant doses has a higher affinity for M2 muscarinic receptors as compared with M3 muscarinic receptors. A potential mechanism by which rapacuronium may potentiate bronchoconstriction is by blockade of M2 muscarinic receptors on prejunctional parasympathetic nerves, leading to increased release of acetylcholine and thereby resulting in M3 muscarinic receptor-mediated airway smooth muscle constriction.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:51415 CAPLUS
DOCUMENT NUMBER: 136:118468
TITLE: Preparation of 2-aryl-2-hydroxyacetic acid ester derivatives as muscarinic M3 receptor antagonists
INVENTOR(S): Ogino, Yoshio; Kurihara, Hideki; Matsuda, Kenji; Numazawa, Tomoshige; Otake, Norikazu; Noguchi, Kazuhito
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 138 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002004402	A1	20020117	WO 2001-JP5987	20010710
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 200171027	A	20020121	AU 2001-71027	20010710
CA 2415468	A1	20030110	CA 2001-2415468	20010710
EP 1302458	A1	20030416	EP 2001-949925	20010710
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2003191316	A1	20031009	US 2003-332617	20030110
US 6846835	B2	20050125		
US 2005065211	A1	20050324	US 2004-983613	20041109
US 7192969	B2	20070320		
US 2007129397	A1	20070607	US 2007-648614	20070103

PRIORITY APPLN. INFO.:

JP 2000-210591	A	20000711
WO 2001-JP5987	W	20010710
US 2003-332617	A3	20030110
US 2004-983613	A3	20041109

OTHER SOURCE(S): MARPAT 136:118468

AB Compds. of the general formula ArC(OH)(R1)CO2A [wherein A is a group of the general formula -B1-N+R2R3R4.X- or -B2-NR5CR6:NR7; Ar is aryl or heteroaryl, any of which may be substituted; B1 and B2 are each an aliphatic hydrocarbon group; R1 is fluorinated cycloalkyl; R2, R3 and R4 are each lower alkyl, or a single bond or alkylene, any of which is bonded to B1, or alternatively R2 and R3 may be united to form alkylene; R5 and R7 are each hydrogen, lower alkyl, or a single bond or alkylene, any of which is bonded to B2; R6 is hydrogen, lower alkyl, or N(R8)R9; R8 and R9 are independently hydrogen or lower alkyl; and X- is an anion] are prepared Thses compds. exhibit selective muscarinic M3 receptor antagonism with little side effects and are suitable for administration by inhalation and useful as therapeutic agents for respiratory system diseases including chronic obstructive pulmonary diseases, chronic bronchitis, asthma, chronic airway obstruction, pulmonary fibrosis, pulmonary emphysema, or rhinitis. Thus, reductive methylation of piperidin-4-yl (2R)-((1R)-3,3-difluoropentyl)-2-hydroxy-2-phenylethanoate by formaldehyde and sodium cyanoborohydride in the presence of ZnCl2 in MeOH at room temperature for 30 min gave 1-methylpiperidin-4-yl (2R)-((1R)-3,3-difluoropentyl)-2-hydroxy-2-phenylethanoate which was quaternized by Me bromide in MeCN at

room temperature for 15 h to give 4-[[(2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylethanoyl]oxy]-1,1-dimethylpiperidinium bromide (I). In a muscarinic receptor M2 and M3 antagonism assay, 4-(((2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylethanoyl)oxy)-1,1-dimethylpiperidinium bromide in vitro exhibited KB of 9.6 nM for inhibiting the carbachol-induced reduction in heart beat in rat right atrium (muscarinic receptor M2 receptor) and that of 0.004 nM for inhibiting the carbachol-induced contraction of trachea (muscarinic receptor M3 receptor) with M2/M3 receptor ratio of 218. An ampule or a powder inhalation formulation containing I were described.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

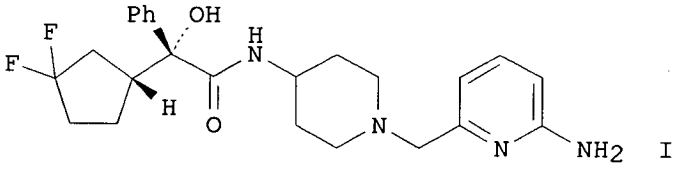
L4 ANSWER 8 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:427889 CAPLUS
DOCUMENT NUMBER: 135:162581
TITLE: Muscarinic receptor -β-adrenoceptor cross-talk in airways smooth muscle
AUTHOR(S): Meurs, Herman; Roffel, Ad F.; Elzinga, Carolina R. S.; Zaagsma, Johan
CORPORATE SOURCE: Department of Molecular Pharmacology, University Centre for Pharmacy, Groningen, 9713 AV, Neth.
SOURCE: Muscarinic Receptors in Airways Diseases (2001), 121-157. Editor(s): Zaagsma, Johan; Meurs, Herman; Roffel, Ad F. Birkhaeuser Verlag: Basel, Switz. CODEN: 69BJUL
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review, with 238 refs., on the cross-talk between muscarinic and β-adrenergic receptor transduction mechanisms involved in the functional antagonism between contractile and relaxing stimuli and the role of this process in altered airway smooth muscle responsiveness in asthma.
REFERENCE COUNT: 238 THERE ARE 238 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:790497 CAPLUS
DOCUMENT NUMBER: 133:350147
TITLE: Processes for the preparation of piperidylmethylpyridine derivatives
INVENTOR(S): Nemoto, Takayuki; Kawasaki, Masashi; Itoh, Takahiro; Mase, Toshiaki
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 42 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066579	A1	20001109	WO 2000-JP2755	20000426

W: AE, AG, AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LV, MA, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 1999-123157 A 19990428
OTHER SOURCE(S): CASREACT 133:350147; MARPAT 133:350147
GI



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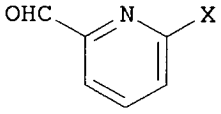

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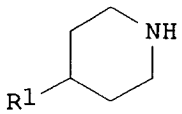
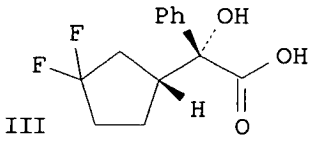
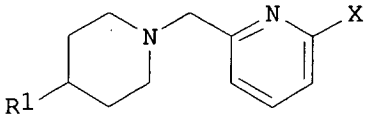




III VII



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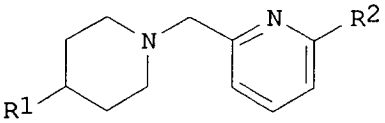


V

AB An industrial process for the preparation of the title compds. (I) or salts thereof is characterized by reacting a compound of general formula (II; X = halo) or a salt thereof with a compound of general formula (III; R1 = optionally protected amino) or a salt thereof under reducing conditions to obtain a compound of general formula (IV; X, R1 = same as above) or salts thereof, reacting this compound or this salt with an aminating agent to obtain a compound of general formula (V; R2 = optionally protected amino) or a salt thereof, freeing at need the compound V or the salt thereof from the

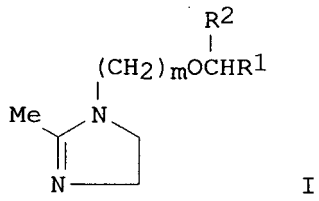
amino-protecting group of R1 and the amino substituent of R2 to obtain compound V (R2 = NH2) (VI) or a salt thereof, condensing the compound V or VI or the salt thereof with compound (VII), and removing the substituent of R2. This process gives in high yields and fewer steps I which is known to exhibit highly selective antagonism against muscarine M3 receptor and to be useful for the treatment or prevention of respiratory, urinary, or digestive tract diseases (no data).

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:457037 CAPLUS
DOCUMENT NUMBER: 133:74018
TITLE: Preparation of 2-methylimidazolines
INVENTOR(S): Ohno, Norio; Endoh, Junichi; Aizawa, Hideyuki
PATENT ASSIGNEE(S): Mitsubishi-Tokyo Pharmaceuticals, Inc., Japan; Miura, Masataka
SOURCE: PCT Int. Appl., 23 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000039096	A1	20000706	WO 1999-JP7327	19991227
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
JP 2003089688	A	20030328	JP 1998-370263	19981225
AU 2000018018	A	20000731	AU 2000-18018	19991227
PRIORITY APPLN. INFO.:			JP 1998-370263 A	19981225
			WO 1999-JP7327 W	19991227

OTHER SOURCE(S): MARPAT 133:74018
GI



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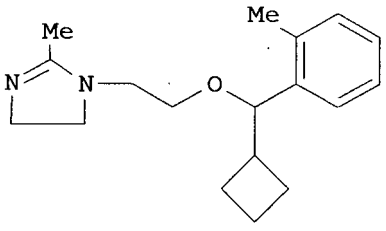


II

AB Title imidazolines [I; wherein R1 is optionally substituted phenyl; R2 is Ph or lower cycloalkyl; and m is 2 or 3] and pharmacol. salts are prepared and exhibit potent and selective antagonism against muscarinic M3 receptor. Thus, title compds. are not only useful as preventive or therapeutic agents for diseases in which muscarinic M3 receptor participates, but also capable of providing safe drugs which can lower the adverse effects on the heart in which muscarinic M3 receptor participates.

The title compound II was prepared and tested.

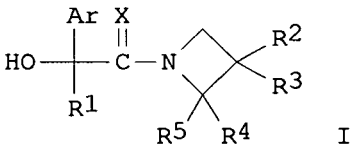
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:368356 CAPLUS
DOCUMENT NUMBER: 133:17372
TITLE: Preparation of 1-acylazetidine derivatives as selective inhibitors of M3-muscarinic receptor
INVENTOR(S): Tsuchiya, Yoshimi; Nomoto, Takashi; Nomoto, Takashi; Kawakami, Kumiko; Ohwaki, Kenji; Nishikibe, Masaru
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 72 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000031078	A1	20000602	WO 1999-JP6497	19991119

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: JP 1998-331040 A 19981120
OTHER SOURCE(S): MARPAT 133:17372
GI



I

AB Compds. represented by general formula [I; wherein Ar is an aryl or heteroaryl group which may optionally bear a substituent selected from the group consisting of halogeno, lower alkyl and lower alkoxy; R1 is optionally fluorinated C3-6 cycloalkyl; R2 and R4 are each hydrogen, -(A1)m-NH-B, or the like; wherein A1 is an optionally lower alkyl-substituted bivalent aliphatic hydrocarbon group; m is 0 or 1; B is hydrogen or C1-6 aliphatic hydrocarbon group optionally having a substituent selected from lower alkyl and aryl; R3 and R5 are each hydrogen, an aliphatic C1-6 hydrocarbon group optionally substituted with lower alkyl, or the like; and X is oxygen or sulfur] are prepared These compds. exhibit selective muscarinic M3 receptor antagonism and are excellent in peroral activities, persistency of action, and in vivo kinetics, thus being useful as treating agents for respiratory, urol. or digestive diseases which have little adverse effect and are safe and efficacious. Thus, 7-benzyl-2,7-diazaspiro[3.5]nonane was condensed with (2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetic acid using 1-hydroxybenzotriazole monohydrate and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in DMF at room temperature for 15 h, followed by hydrogenolysis of the product over 20% Pd(OH)2 in MeOH under H for 2 h to give 2-{(2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetyl}-2,7-diazaspiro[3.5]nonane (II). II in vitro showed IC50

of 180 and 1.9 for inhibiting the binding of [3H]-N-methylscopolamine to muscarine M2 and M3 receptor, resp. Pharmaceutical formulations containing II were prepared

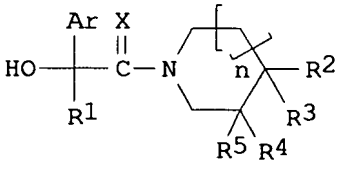
REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:511138 CAPLUS
DOCUMENT NUMBER: 131:144516
TITLE: Preparation of N-acyl cyclic amine derivatives as selective antagonists of muscarine M3 receptor
INVENTOR(S): Tsuchiya, Yoshimi; Nomoto, Takashi; Ohsawa, Hirokazu; Kawakami, Kumiko; Ohwaki, Kenji; Nishikibe, Masaru
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 112 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940070	A1	19990812	WO 1999-JP462	19990203
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9900831	A	19990803	ZA 1999-831	19990203
CA 2317444	A1	19990812	CA 1999-2317444	19990203
AU 9922986	A	19990823	AU 1999-22986	19990203
AU 745995	B2	20020411		
TR 200002241	T2	20001121	TR 2000-2241	19990203
EP 1061076	A1	20001220	EP 1999-902825	19990203
EP 1061076	B1	20041208		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9908351	A	20011120	BR 1999-8351	19990203
HU 2001002404	A2	20011128	HU 2001-2404	19990203
EE 200000458	A	20020215	EE 2000-458	19990203
AT 284389	T	20041215	AT 1999-902825	19990203
JP 3613179	B2	20050126	JP 2000-530500	19990203
ES 2235458	T3	20050701	ES 1999-902825	19990203
US 6140333	A	20001031	US 1999-244985	19990204
HR 2000000495	A1	20030630	HR 2000-495	20000721
HR 2000000495	B1	20051231		
MX 2000PA07615	A	20010219	MX 2000-PA7615	20000803
NO 2000003945	A	20001003	NO 2000-3945	20000804
BG 104663	A	20010928	BG 2000-104663	20000804

PRIORITY APPLN. INFO.:
JP 1998-38063 A 19980204
JP 1998-228726 A 19980729
WO 1999-JP462 W 19990203

OTHER SOURCE(S): MARPAT 131:144516
GI



I

AB The title (2-aryl-2-hydroxyacetyl)piperidines and -pyrrolidines represented by general formula [I; wherein Ar represents aryl or heteroaryl optionally substituted by halogeno, lower alkyl or lower alkoxy; R1 represents optionally fluorinated C3-6 cycloalkyl; R2 and R4 represent each hydrogen, -(A1)m-NH-B, etc.; wherein A1 represents optionally lower alkyl-substituted bivalent C1-8 aliphatic hydrocarbon group; m is 0 or 1; B represents H or C1-6 aliphatic hydrocarbon group optionally substituted by a group selected from lower alkyl or aryl; R3 and R5 represent each hydrogen, aliphatic C1-6 hydrocarbyl optionally substituted by lower alkyl, etc.; n is 0 or 1; and X represents oxygen or sulfur] are prepared These compds. have selective muscarine M3 receptor antagonism and are excellent in oral activity, duration of action and dynamics in vivo, which makes them useful as safe and efficacious drugs with little side effects for treating respiratory diseases, urol. diseases, or digestive diseases such as chronic obtrusive lung diseases, chronic bronchitis, asthma, chronic respiratory obstruction, pulmonary fibrosis, pulmonary emphysema, irritable bowel syndrome, spasmodic colitis, duodenal ulcer, spasm of digestive tract, exasperation of digestive tract motility, diverticulitis, pain accompanied by smooth muscle twitch of digestive organs, nervous pollakiuria (frequent urination), nocturnal enuresis, unstable bladder, bladder contracture, chronic cystitis, urinary incontinence, urinary urgency, or car sickness. Thus, 2-benzyloxycarbonyl-8-tert-butoxycarbonyl-1-methyl-2,8-diazabicyclo[4.5]decane was treated with 10% HCl in MeOH, condensed with (2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid using 1-hydroxybenzotriazole and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride in CHCl3 at room temperature for 3 h, and then hydrogenolyzed over 10% Pd-C in MeOH/EtOAc to give (1R)- and (1S)-8-{(2R)-2-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetyl}-1-methyl-2,8-diazabicyclo[4,5]decane (II). (1S)-II inhibited the binding of [3H]-N-methylscopolamine to muscarine M2 and M3 receptor with Ki of 21 and 0.26 nM, resp. Pharmaceutical formulations (e.g tablet) containing 4-amino-1-{(2R)-2-((1R)-3,3-difluorocyclopentyl)-2-hydroxy-2-phenylacetyl}piperidine hydrochloride were prepared

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:269311 CAPLUS
TITLE: Assessment of cardiac sympathetic regulation by respiratory-related arterial pressure variability in the rat
AUTHOR(S): Yang, Cheryl C. H.; Kuo, Terry B. J.
CORPORATE SOURCE: Department of Physiology, Tzu Chi College of Medicine and Humanities, Hualien, 970, Taiwan
SOURCE: Journal of Physiology (Cambridge, United Kingdom) (1999), 515(3), 887-896
CODEN: JPHYA7; ISSN: 0022-3751
PUBLISHER: Cambridge University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 1. Mech. ventilation evokes a corresponding arterial pressure variability (APV) which is decreased by β-adrenoceptor antagonism. Therefore, in this study we set out to determine whether the respiratory-related APV can be used to assess cardiac sympathetic tone. 2. Computer-generated broad-band mech. ventilation (0-3 Hz) was applied to Sprague-Dawley rats that had been anesthetized with ketamine and paralysed with pancuronium. APV and its relationship to lung volume variability (LVV-APV) was systematically quantified with auto- or cross-spectral frequency domain anal. 3. APV and LVV-APV transfer magnitudes between 0.5 and 1.5 Hz showed dose-dependent suppression by propranolol from 0.01 to 1 mg kg-1, while the static value of arterial pressure remain unchanged. Stroke volume variability, assessed by the use of a pulse contour method, exhibited a similar pattern of suppression by propranolol. In contrast, heart rate variability was not lowered with propranolol. 4. The effect of propranolol on respiratory -related APV persisted even in the presence of combined α-adrenoceptor and muscarinic receptor blockade by phentolamine and atropine. 5. The frequency range of 0.5-1.0 Hz was optimal for LVV-APV transfer magnitude to correlate with cardiac sympathetic tone. 6. We conclude that respiratory-related APV may provide a valid assessment of cardiac sympathetic regulation which is independent of parasympathetic and vascular sympathetic influences in ketamine-anesthetized and pos. pressure-ventilated rats.

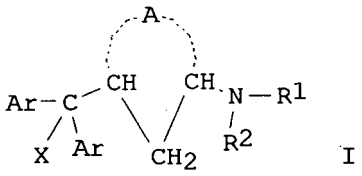
REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1999:96204 CAPLUS
DOCUMENT NUMBER: 130:153567
TITLE: Preparation of aminocycloalkane compounds as M3 receptor antagonists
INVENTOR(S): Ohno, Norio; Nakano, Masakazu; Endoh, Jun-ichi; Miura, Masataka; Aizawa, Hideyuki; Fukuzaki, Athushi; Seida, Keiichi
PATENT ASSIGNEE(S): Tokyo Tanabe Company Limited, Japan
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9905095	A1	19990204	WO 1998-JP3299	19980723
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HU, ID, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2296329	A1	19990204	CA 1998-2296329	19980723
AU 9883571	A	19990216	AU 1998-83571	19980723
EP 999205	A1	20000510	EP 1998-933913	19980723
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: JP 1997-197646 A 19970724
WO 1998-JP3299 W 19980723

OTHER SOURCE(S): MARPAT 130:153567
GI



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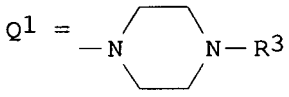

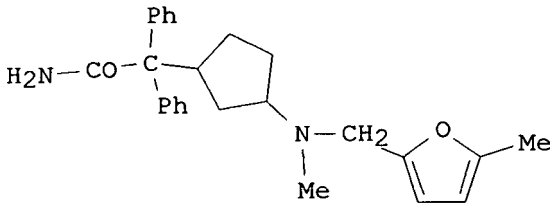

II

AB The title compds. I [A = (CH2)m; Ar represents optionally substituted Ph or thienyl; X represents cyano or carbamoyl; R1 and R2 each independently represents hydrogen, lower alkyl, etc., or R1 and R2 together with the nitrogen atom bonded thereto represent Q1 (wherein R3 represents hydrogen, lower alkyl, etc.); and m is 2, 3, or 4] are prepared The compds. have a highly selective antagonistic action on a muscarine M3 receptor. In an in

vitro test for antagonism of ileum and bladder M3 receptors, the title compound (-)-II showed the pA2 values of 9.3 and 8.5, resp.

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:315821 CAPLUS
DOCUMENT NUMBER: 129:49477
TITLE: Contractile effect of 6β-acetoxy nortropane on human and guinea pig airways
AUTHOR(S): Zhang, Yong; Moreau, Joelle; Molimard, Mathieu; Naline, Emmanuel; Bisson, Alain; Advenier, Charles
CORPORATE SOURCE: Faculté Medecine Paris-Ouest, Paris, 75270, Fr.
SOURCE: Zhongguo Yaoli Xuebao (1998), 19(3), 211-217
CODEN: CYLPDN; ISSN: 0253-9756
PUBLISHER: Kexue Chubanshe
DOCUMENT TYPE: Journal
LANGUAGE: English

AB AIM: to study the effects of 6β-acetoxy nortropane (6β-AN) on the isolated human bronchus and guinea pig trachea. METHODS: the contractile effect of 6β-AN was studied with 4 different muscarinic receptor antagonists on airway strips and inositol phosphates (IP) accumulation in human bronchi was determined by HPLC with radioactivity flow detector. RESULTS: (1) the maximal contractile effect of 6β-AN was lower than that of acetylcholine (ACh) on the human bronchus and equal to that of ACh on the guinea pig trachea. 6β-AN was more potent than ACh on both prepns. (68 and 245 times, resp.). (2) The contractile effect of 6β-AN was inhibited by atropine (1 - 100 nmol·L-1) or para-fluoro-hexahydro-siladifenidol (0.01 - 1 μmol · L-1), but not by methoctramine (Met, 0.3 - 3 μmol · L-1) or pirenzepine (0.01 - 0.1 μmol · L-1), and was not enhanced by tacrine (0.1 - 10 μmol·L-1) or by epithelium removal. (3) The 6β-AN induced-contraction was accompanied by an increase of IP levels in isolated human bronchial tissues. (4) 6β-AN had an inhibitory effect on isoprenaline (Iso)-induced relaxation, which was abolished or reduced by Met 0.3 μmol · L-1. CONCLUSION: 6β-AN exerts a potent contractile effect involving muscarinic M3 receptor stimulation on airway smooth muscle. Muscarinic M2 receptor stimulation is furthermore partially involved in the antagonism by 6β-AN on the Iso-induced relaxation of the guinea pig trachea.

REFERENCE COUNT: 15 THERE ARE 15 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1998:112344 CAPLUS
DOCUMENT NUMBER: 128:192550
TITLE: Preparation of fluorinated 1,4-disubstituted piperidine derivatives as muscarinic receptor antagonists
INVENTOR(S): Tsuchiya, Yoshimi; Nomoto, Takashi; Ohsawa, Hirokazu; Kawakami, Kumiko; Ohwaki, Kenji; Nishikibe, Masaru
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9805641	A1	19980212	WO 1997-JP2600	19970728
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW				
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CA 2261680	C	20050308		
AU 9736351	A	19980225	AU 1997-36351	19970728
AU 716050	B2	20000217		
EP 930298	A1	19990721	EP 1997-933037	19970728
EP 930298	B1	20021218		
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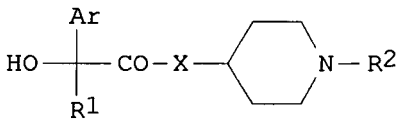
BR 9711108	A	19990817	BR 1997-11108	19970728
CN 1226888	A	19990825	CN 1997-196911	19970728
HU 9902381	A2	19991129	HU 1999-2381	19970728
TR 9900204	T2	20000121	TR 1999-204	19970728
JP 2000169449	A	20000620	JP 2000-27462	19970728
JP 3282618	B2	20020520		
JP 2000178231	A	20000627	JP 2000-27461	19970728
JP 3282617	B2	20020520		
JP 3063164	B2	20000712	JP 1998-507794	19970728
TR 200001482	T2	20001121	TR 2000-1482	19970728
NZ 333842	A	20010525	NZ 1997-333842	19970728
AT 229941	T	20030115	AT 1997-933037	19970728
ES 2188961	T3	20030701	ES 1997-933037	19970728
US 5948792	A	19990907	US 1997-903768	19970731
ZA 9706813	A	19980211	ZA 1997-6813	19970831
KR 2000022214	A	20000425	KR 1998-710633	19981224
NO 9900472	A	19990201	NO 1999-472	19990201
US 6040449	A	20000321	US 1999-290607	19990413
PRIORITY APPLN. INFO.:			JP 1996-219436 A	19960801
			JP 1997-53979 A	19970221
			JP 1998-507794 A3	19970728
			WO 1997-JP2600 W	19970728
			US 1997-903768 A3	19970731

OTHER SOURCE(S): MARPAT 128:192550
GI



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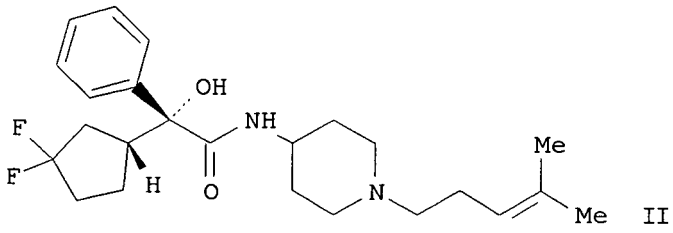


II

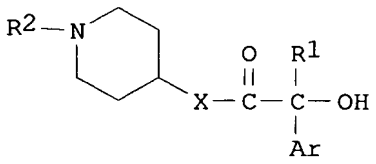
AB The title compds. [I; Ar = (un)substituted aryl or heteroaryl etc.; R1 = C1-3 cycloalkyl in which 1-4 arbitrary H may be substituted by F; R2 = saturated or unsatd., aliphatic C5-15 hydrocarbyl in which 1-6 arbitrary H may be substituted by F, aralkyl, arylalkenyl, or heteroarylalkyl or heteroarylalkenyl having 1-2 heteroatoms selected from the group consisting of N, O, S; X = O, NH] or pharmaceutically acceptable salts thereof are prepared Because of having selective muscarinic receptor antagonism and being excellent in oral activity, persistence of the action and dynamic in vivo, I are useful as efficacious and safe remedies or preventives with little side effects for respiratory, urol. and digestive diseases. Thus, (2R)-[(1R)-3,3-difluorocyclopentyl]-2-hydroxy-2-phenylacetic acid (preparation given) was reacted with 4-amino-1-(4-methyl-3-pentenyl)piperidine (preparation given) in the presence of 1,1'-carbonyldiimidazole and 4-dimethylaminopyridine to give the title compound (II), which showed ED50 of 0.033 mg/Kg against muscarinic receptor antagonism when tested with rat.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:805726 CAPLUS
DOCUMENT NUMBER: 128:48143
TITLE: Preparation of 1,4-disubstituted piperidine derivatives as muscarine M3 receptor inhibitors
INVENTOR(S): Tsuchiya, Yoshimi; Nomoto, Takashi; Ohsawa, Hirokazu; Kawakami, Kumiko; Ohwaki, Kenji; Nishikibe, Masaru
PATENT ASSIGNEE(S): Banyu Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9745414	A1	19971204	WO 1997-JP1770	19970527
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9727931	A	19980105	AU 1997-27931	19970527
PRIORITY APPLN. INFO.:			JP 1996-159176 A	19960531
			WO 1997-JP1770 W	19970527

OTHER SOURCE(S): MARPAT 128:48143
GI



I

AB The title compds. [I; Ar = heteroaryl having one or two heteroatoms selected from the group consisting of N, O and S and optionally fused to aryl or benzene (wherein each H on the aryl and heteroaryl rings may be substituted by lower alkyl, halo, alkoxy, amino or hydroxymethyl); R1 = C3-6 cycloalkyl having one or two OH groups on the ring; R2 = heteroarylalkyl having one or two heteroatoms selected from the group consisting of N, O and S and optionally fused to saturated or unsatd. aliphatic C5-15 hydrocarbon, arylalkenyl and heteroarylalkyl rings may be substituted by lower alkyl, halo, lower alkoxy, amino or hydroxymethyl, etc.; X = O or NH.] and pharmaceutically acceptable salts thereof are prepared I, having a selective muscarine M3 receptor antagonism, are useful as safe remedies or preventives with little side effects for respiratory diseases such as asthma, chronic respiratory obstruction and pulmonary fibrosis; urol. diseases in association with urination disorders such as frequent urination, urgency of micturition and urinary incontinence; and digestive diseases such as irritable bowel syndrome and convulsion or motor hyperenergia of digestive tracts. Thus, N-[1-(4-methyl-3-pentenyl)piperidin-4-yl]-2-(4-oxocyclohexyl)-2-hydroxy-2-phenylacetamide (preparation given) was treated with NaBH4 to give I [Ar = Ph, R1 = 4-hydroxycyclohexyl, X = NH, R2 = (CH2)2CH:CMe2]. I were tested and showed muscarine M3 receptor inhibitory activity in vitro and in vivo.

L4 ANSWER 18 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:725322 CAPLUS
DOCUMENT NUMBER: 128:21811
TITLE: Pretreatment with antibody to eosinophil major basic protein prevents hyperresponsiveness by protecting neuronal M2 muscarinic receptors in antigen-challenged guinea pigs
AUTHOR(S): Evans, Christopher M.; Fryer, Allison D.; Jacoby, David B.; Gleich, Gerald J.; Costello, Richard W.
CORPORATE SOURCE: Department of Environmental Health Sciences, School of Hygiene and Public Health, Johns Hopkins University, Baltimore, MD, 21205, USA
SOURCE: Journal of Clinical Investigation (1997), 100(9), 2254-2262
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In antigen-challenged guinea pigs there is recruitment of eosinophils into the lungs and to airway nerves, decreased function of inhibitory M2 muscarinic autoreceptors on parasympathetic nerves in the lungs, and airway hyperresponsiveness. A rabbit antibody to guinea pig eosinophil major basic protein was used to determine whether M2 muscarinic receptor dysfunction, and the subsequent hyperresponsiveness, are due to antagonism of the M2 receptor by eosinophil major basic protein. Guinea pigs were sensitized, challenged with ovalbumin and hyperresponsiveness, and M2 receptor function tested 24 h later with the muscarinic agonist pilocarpine. Antigen-challenged guinea pigs were hyperresponsive to elec. stimulation of the vagus nerves compared with controls. Likewise, loss of M2 receptor function was demonstrated since the agonist pilocarpine inhibited vagally-induced bronchoconstriction in control but not challenged animals. Pretreatment with rabbit antibody to guinea pig eosinophil major basic protein prevented hyperresponsiveness, and protected M2 receptor function in the antigen-challenged animals without inhibiting eosinophil accumulation in the lungs or around the nerves. Thus, hyperresponsiveness is a result of inhibition of neuronal M2 muscarinic receptor function by eosinophil major basic protein in antigen-challenged guinea pigs.
REFERENCE COUNT: 54 THERE ARE 54 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 19 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1994:96865 CAPLUS
DOCUMENT NUMBER: 120:96865
TITLE: Increased cholinergic antagonism underlies impaired β-adrenergic response in ovalbumin-sensitized guinea pigs
AUTHOR(S): Wills-Karp, Marsha; Gilmour, Matthew I.
CORPORATE SOURCE: Sch. Hyg. Public Health, Johns Hopkins Univ., Baltimore, MD, 21205, USA
SOURCE: Journal of Applied Physiology (1993), 74(6), 2729-35
CODEN: JAPHEV; ISSN: 8750-7587
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The goal of this study was to determine if the hyporesponsiveness to β-adrenoceptor stimulation observed in ovalbumin-sensitized tracheal smooth muscle is due to increased cholinergic muscarinic tone or to a defect in the β-adrenergic cascade itself. The authors examined the effects of ovalbumin-sensitization on the responsiveness of guinea pig tracheas to agents that mediate relaxation at various steps in the β-adrenergic cascade when the tracheal tissue was preconstricted with either carbachol or histamine. Ovalbumin sensitization caused significant redns. in the maximal relaxations both to the β-adrenergic agonist isoproterenol and to PGE2 in guinea pig trachealis when the tracheal tissue was preconstricted with the muscarinic agonist carbachol. In contrast, sensitization had no effect on the ability of PGE2 and isoproterenol to relax histamine contractions. Preconstricting the tissues with increasing concns. of KCl reduced the effectiveness of isoproterenol to relax equally airway tissues from both sensitized and control animals. Forskolin-induced relaxations of trachealis muscle were not altered with sensitization. When tracheal tissues were precontracted with increasing concns. of carbachol, the effectiveness of isoproterenol and PGE2 to relax airway tissues decreased. Functional antagonism of relaxations by muscarinic agonists was enhanced in the sensitized tissues, since the concentration of carbachol necessary to reduce β-adrenoceptor-induced relaxations to the same degree as in the control animals was a log dose lower. These results suggest that the impaired β-adrenoceptor response in sensitized tissues is not due to an intrinsic defect in the β-adrenergic cascade but to an enhancement of a muscarinic cholinergic pathway.

L4 ANSWER 20 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1991:200242 CAPLUS
DOCUMENT NUMBER: 114:200242
TITLE: Reserpine-induced post-receptor reduction in muscarinic-mediated airway smooth muscle contraction
AUTHOR(S): Gardier, Robert W.; Blaxall, Howard S.; Killian, Lawrence N.; Cunningham, John
CORPORATE SOURCE: Sch. Med., Wright State Univ., Dayton, OH, 45435, USA
SOURCE: Life Sciences (1991), 48(18), 1705-13
CODEN: LIFSAK; ISSN: 0024-3205
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Radioligand binding was conducted on airways of the rat and human, surgically subdivided into trachea, lung airways, and parenchyma. [3H]quinuclidinyl benzilate ([3H]QNB) bound uniformly to receptors in sep. sections of the rat and human airway. Receptor densities generally were ranked: lung airways > trachea > parenchyma. Receptor subtypes were identified mostly by pirenzepine displacement of bound [3H]QNB. The rat trachea and the rat and human lung airways had a uniformly low affinity for pirenzepine while rat and human parenchyma demonstrated both high and low affinity pirenzepine binding. Inhibition of methacholine-stimulated smooth muscle contraction by the M1 receptor antagonist, pirenzepine, and M2 receptor antagonist, gallamine, was studied in rat trachea and bronchus in vitro. Schild plot pA2 values were compatible with low potency antagonism, thereby favoring the presence of M3 receptors at these smooth muscle sites. Reserpine treatment of rats (0.5 mg/kg/day for 7 days) produced a decrease in peak tension in response to methacholine without changing the muscarinic receptor character (Kd [3H]QNB), population d. (Bmax in fmol/mg protein), or function (methacholine EC50). These results indicate that muscarinic receptor heterogeneity exists in the airway of both laboratory rat and man. While the muscarinic receptor subserving airway smooth muscle contraction appears to be the M3 subtype, decreased contractile responses to methacholine by trachea and bronchus from reserpine-treated rats were receptor independent.

L4 ANSWER 21 OF 21 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1986:401118 CAPLUS
DOCUMENT NUMBER: 105:1118
TITLE: Tachykinin antagonists and mucociliary activity
AUTHOR(S): Lindberg, Sven; Mercke, Ulf
CORPORATE SOURCE: Dep. Oto-Rhino-Laryngol., Univ. Hosp., Lund, S-221 85, Swed.
SOURCE: Fernstroem Foundation Series (1985), 6(Tachykinin Antagonists), 203-10
CODEN: FFOSDF; ISSN: 0167-7004
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Of 3 substance P(SP) antagonists tested, [D-Pro2,D-Trp7,9]SP (I) [80434-86-2] most actively inhibited the mucociliary activity in rabbit maxillary sinus. Spantide [91224-37-2] also inhibited the mucociliary response to SP [33507-63-0], but this antagonism was very short-lived. Spantide antagonism of SP action in other organs and species was discussed. The 3rd antagonist [D-Arg1,D-Pro2,D-Trp7,9,Leu11]SP [84676-91-5] was relatively inactive, and apparently the D-Pro2 substitution had little effect in this model. Methacholine produced the expected acceleration of mucociliary activity in the presence of SP blockade, and it was assumed that I did not interfere with responses mediated through muscarinic receptors. I reversibly inhibited C-fiber stimulation by bradykinin and capsaicin and also inhibited antidromic nerve stimulation of mucociliary activity; thus, SP peptides may be included in regulating mucociliary activity. The mucociliary irritation response to cigarette smoke was suppressed not only by atropine but also by I and capsaicin treatment. Irritation accelerating mucociliary activity was discussed with reference to a reflex involving sensory SP-containing C-fibers (afferent pathway) and cholinergic effect on neurons (efferent pathway).

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L2             0 S L1 AND RESPITORY?
L3           468 S L1 AND RESPIRATORY?
L4            21 S L3 AND ANTAGONISM?

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